Acute Myelomonocytic Leukemia Presenting as a Benign-Appearing Cutaneous Eruption

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• **Aleukemic leukemia cutis is a rare condition in which patients have skin lesions containing leukemic cells before evidence of leukemia can be detected in the peripheral blood. There are only 23 cases of this phenomenon documented in the English literature. We describe a 62-year-old woman who developed a diffuse, clinically benign-appearing cutaneous eruption, which histologically showed an atypical infiltrate of cells, 4 months before leukemic cells were found in her peripheral blood and the diagnosis of acute myelomonocytic leukemia was made by bone marrow aspiration. This case illustrates the difficulty in diagnosing leukemia cutis from examination of routine histologic sections and the importance of specialized marker studies in determining the cause of an atypical cellular infiltrate of the skin. It also illustrates how leukemia cutis can masquerade as a clinically benign-appearing cutaneous eruption in a seemingly healthy patient with normal blood parameters.**

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The cutaneous manifestations of leukemias can be divided into nonspecific lesions (leukemids) containing no leukemic cells, and specific lesions (leukemia cutis). Leukemids (the term was coined by Audry[1]) may result from immunologic responses to tumor antigens and include hemorrhagic lesions, generalized pruritus, exfoliative erythroderma, pyoderma gangrenosum, urticaria, erythema multiforme, erythema nodosum, panniculitis, hyperpigmentation, and morbilliform eruptions. Nonspecific cutaneous lesions are found in approximately 30% of patients suffering from leukemia.[2] Leukemia cutis, in which leukemic cells are found in skin lesions, is much less common. The incidence varies with the type of leukemia; the myeloid leukemias are marked by cutaneous involvement more frequently than other types of leukemia. Skin involvement typically occurs late in the course of leukemia cutis. However, occasional cases of leukemic infiltrates appearing in the skin prior to peripheral blood involvement (aleukemic leukemia cutis) can be found in the literature.

We report a case of acute myelomonocytic leukemia that presented as a clinically benign-appearing cutaneous eruption 4 months before evidence of leukemia could be detected in the peripheral blood.

REPORT OF A CASE

A 62-year-old woman, originally from Ecuador, presented to the Dermatology Clinic of the Columbia-Presbyterian Medical Center, New York, NY, with a 2-month history of a nonpruritic eruption on her chest, abdomen, back, buttocks, arms, and thighs, with occasional mild involvement of the lateral aspects of her face. She reported that the eruption began on her upper torso and spread to the other areas over approximately 2 weeks, and that individual lesions waxed and waned over several days and were stress-related. Her medical history was noncontributory, and her review of systems was negative. She was receiving no medications.

Physical examination revealed hundreds of erythematous to violaceous 2- to 4-mm dome-shaped papules randomly distributed over the above-mentioned areas (Figs 1 and 2). Initially, her face was free of lesions. On subsequent clinic visits, 20 to 50 similar lesions were occasionally noted on the lateral aspects of her face. The lesions were, in fact, transient, but the patient suffered from successive crops of lesions. The results of her physical examination were otherwise unremarkable. She had no palpable lymphadenopa-

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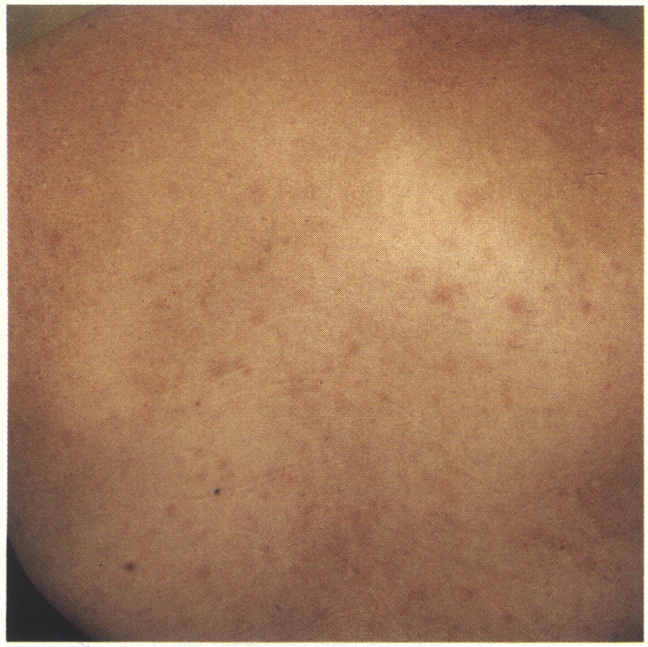

Fig 1.—The patient's upper back shows numerous papules arranged in a diffuse fashion.

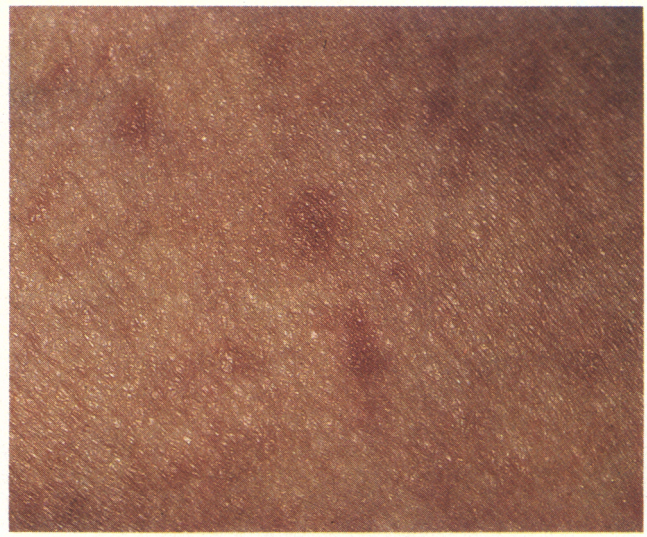

Fig 2.—The lesions measure 2 to 4 mm in diameter and are pink to violaceous.

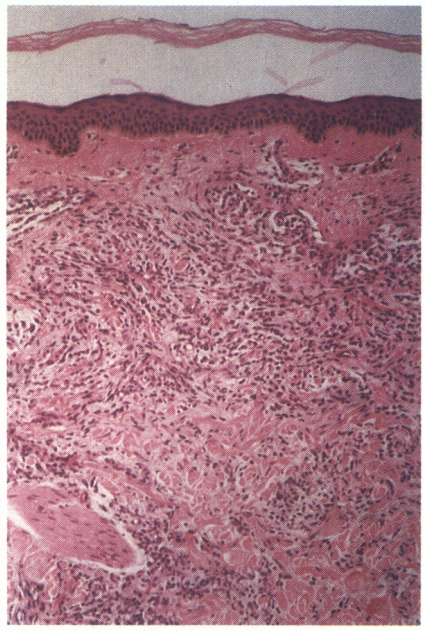

Fig 3.—There is a thin zone of connective tissue separating the normal-appearing epidermis from a dermal infiltrate composed of atypical mononuclear cells (hematoxylin-eosin, ×100).

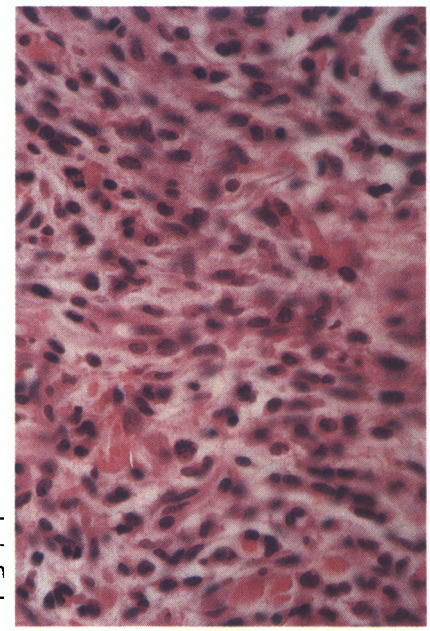

Fig 4.—The atypical cells are hyperchromatic with large nuclei. They infiltrate between collagen bundles in "single file" fashion (hematoxylin-eosin, ×400).

thy, hepatosplenomegaly, or gingival hypertrophy.

Biopsy specimens showed a grenz zone of normal connective tissue separating normal epidermis from a diffuse infiltrate of atypical mononuclear cells in the upper half of the dermis. The cells were arranged in strands and cords. Some cells had kidney bean–shaped nuclei, and there were scattered mitotic figures (Figs 3 and 4). Results of immunoperoxidase studies were positive for the common leukocyte antigen, indicating that the atypical cells were of hematopoietic origin.

The patient's hemoglobin was 141 g/L; platelet count, 357×10^9/L; and white blood cell count, 5.5×10^9/L, with 0.35 polycytes, 0.01 band cells, 0.49 lymphocytes, 0.11 monocytes, and 0.04 eosinophils. Her chemistry profile was normal, and her erythrocyte sedimentation rate was 16 mm/h.

Skin biopsies for monoclonal antibody studies were performed; the cells in the infiltrate were positive for Leu-1 and Leu-9 but negative for CD3, CD4, and CD8, suggesting an atypical T-cell lymphoma. Her complete blood cell count at this time (3 months after developing the eruption and 1 month after presentation to our clinic) was essentially unchanged: hemoglobin, 140 g/L; platelets, 274×10^9/L; and leukocytes, 5.2×10^9/L, with 0.25 polycytes, 0.02 band cells, 0.62 lymphocytes, 0.06 monocytes, and 0.05 eosinophils. The patient was asymptomatic except for the rash.

Bone marrow aspiration was performed, and the major-

ity of the cells in her marrow expressed myeloid antigens MY4, Mol, and LEUM-1, consistent with a diagnosis of acute myelomonocytic leukemia (French-American-British M4).[3] A repeated skin biopsy specimen was studied for AML1-99, AML2-23, PM81, and HL60-251. The cellular infiltrate showed surface immunoreactivity with PM81 and some weak immunoreactivity with AML1-99, consistent with a myeloid infiltrate.[4] On the day of the bone marrow aspiration (2 months after presenting to our clinic), her peripheral blood was unequivocally abnormal for the first time, with the following values: hemoglobin, 100 g/L; platelets, 212×10^9/L; and leukocytes, 2.9×10^9/L, with 0.12 polycytes, 0.38 lymphocytes, 0.10 atypical lymphocytes, and 0.40 monocytes. Her chemistry profile remained normal, but her erythrocyte sedimentation rate rose to 83 mm/h. One week later, her white blood cell count was 3.6×10^9/L, with 0.07 polycytes, 0.02 band cells, 20.0 metamyelocytes, 0.10 blast cells, 0.30 lymphocytes, 0.48 monocytes, and 0.01 eosinophils. She still reported feeling fine.

Treatment with cytarabine and daunorubicin was begun. Her skin lesions regressed completely within 2 days. Undiagnosed fevers were treated with antibiotics, and anemia and thrombocytopenia were treated with packed red blood cell and platelet transfusions. One week after completion of the first course of chemotherapy, bone marrow aspiration revealed no evidence of leukemia. Two weeks later, she was noted to have 100 to 200 erythematous papules on the lateral aspects of her face, neck, shoulders, upper torso, and upper arms. Skin biopsy again revealed an infiltrate of atypical cells. Bone marrow aspiration showed no atypical cells. She was treated with high-dose cytarabine and asparaginase, with rapid resolution of all cutaneous lesions. She subsequently developed nadir sepsis with *Escherichia coli* and *Serratia marcescens* and a lesion of ecthyma gangrenosum of her left axilla, the culture of which yielded *S marcescens*. Her infection gradually resolved with antibiotic therapy.

On a subsequent outpatient follow-up visit, she was again noted to have recurrence of the erythematous papular eruption, primarily on her arms. Chemotherapy with oral 6-thioguanine was instituted and resulted in resolution of the skin lesions. Subsequently, she was maintained on intermittent maintenance therapy with oral 6-thioguanine. Follow-up bone marrow aspiration showed mild myeloid immaturity without evidence of overt leukemia. She is currently receiving no therapy, her blood counts are normal, and her skin remains clear.

COMMENT

Leukemia cutis is a cutaneous eruption in which leukemic cells are present in the skin lesions. The incidence of leukemia cutis varies with the type of leukemia; it has been reported in 10% to 50% of patients with monocytic leukemia, and in 6% to 20% of those with granulocytic and lymphocytic leukemias.[5] The clinical picture of leukemia cutis is highly variable and includes macules, papules, nodules, plaques, ecchymoses, palpable purpura, ulcers, erythroderma, bullae, and gingival hypertrophy.[6] Leukemia cutis is not a clinical diagnosis; biopsy is required. Routine hematoxylin-eosin staining of biopsy specimens reveals an atypical cellular infiltrate, but frequently additional studies, such as with monoclonal antibodies, are required to characterize the cells.

Aleukemic leukemia cutis is a form of leukemia cutis in which, initially, no leukemic cells are found in the blood and in which the total white blood cell count is normal or reduced.[7] A retrospective study revealed that 55% of patients with leukemia cutis developed skin lesions 1 month to several years after the diagnosis was made, 38% had concomitant involvement, and 7% had specific skin lesions preceding involvement of peripheral blood.[6] A review of the English literature reveals only 23 verified cases of leukemia cutis developing before involvement of the peripheral blood. These included 5 cases of acute myelomonocytic leukemia,[8-12] 2 of acute monocytic leukemia,[13,14] 9 of acute granulocytic leukemia,[6,15-17] 4 of chronic lymphocytic leukemia,[6] and 3 of acute lymphocytic leukemia.[18-20]

Our case is an example of the rare occurrence of leukemia presenting as a benign-appearing cutaneous eruption in a patient with no systemic manifestations or complaints and with normal blood parameters. When we first saw the patient, the clinical differential diagnosis included viral exanthem, drug eruption, secondary syphilis, urticaria, sarcoidosis, atypical pityriasis rosea, and atypical lymphomatoid papulosis. Routine histologic sections of biopsy specimens showed an atypical cellular infiltrate. The arrangement and cytology of the cells suggested metastatic carcinoma, leukemia, or lymphoma. Immunoperoxidase studies confirmed the hematopoietic origin of the cells but gave confusing results, suggestive of an atypical T-cell lymphoma.

The diagnosis of acute myelomonocytic leukemia in our patient was made by bone marrow aspiration. We have no way of knowing if the diagnosis could have been made earlier if the marrow aspiration had been performed sooner. Initially, the panel of monoclonal antibodies used to study the atypical cutaneous infiltrate did not include myeloid markers. Subsequent skin biopsy samples were studied with an expanded panel of monoclonal antibodies, and the myeloid origin of the infiltrate was confirmed. This illustrates the importance of using a panel of monoclonal antibodies, including myeloid markers, in ascertaining the nature of a cutaneous lesion of hematopoietic origin. Although cells of lymphocytic origin are found in the vast majority of lymphoreticular malignancies involving the skin (ie, cutaneous T-cell lymphoma), the use of markers that primarily stain cells of lymphocytic origin can result in a misdiagnosis. Cross-reactivity between lymphoid and myeloid cells may occur with Leu-1 and the other antibodies initially used to evaluate the skin biopsy specimen.[21,22]

It is puzzling that leukemic cells can be found in the skin when they cannot be detected in the peripheral blood. Even after the diagnosis of acute myelomonocytic leukemia was made, no suspicious-looking cells could be found on review of the early peripheral smears. The frequency with which acute myelomonocytic leukemia localizes in the skin does not correlate with the peripheral white blood cell count,[23] suggesting that cutaneous factors or specific characteristics of the leukemic cells are important determinants of cutaneous localization.[24]

In summary, our case demonstrates several impor-

tant points: (1) leukemia can present as a cutaneous eruption; (2) the eruption may be nonspecific and benign-appearing; (3) the eruption may precede peripheral blood involvement and other evidence of systemic illness by months; (4) routine histologic sections are insufficient for classification of an atypical cellular infiltrate; and (5) although most cutaneous eruptions of lymphoreticular origin are lymphocytic, monoclonal antibodies specific for myeloid cells must be included in the panel to prevent a delay in diagnosis and specific therapy.

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